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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte VERA MAHLER, SUSANNE VRTALA,
ROLAND SUCK, OLIVER CROMWELL, HELMUT FIEBIG,
DIETRICH KRAFT, and RUDOLF VALENTA

Appeal 2009-012959
Application 10/026,931
Technology Center 1600

Before TONI R. SCHEINER, DEMETRA J. MILLS, and ERIC GRIMES, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 33, 34, 37-41, 43-46, 48-50, and 52-60.[2] The claims have been rejected as lacking enablement, lacking adequate written descriptive support, as anticipated, and as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claim 33 is representative of the subject matter on appeal:

33. A method of treating or preventing a human IgE-mediated allergic disorder resulting from exposure to the major allergens of alder, hazel and birch, comprising

periodically administering for a number of times to a patient in need thereof, a composition comprising one or more immunotherapeutic agents derived from Bet v 1, which induce IgE-blocking antibodies and wherein the allergenic activity of the derivative is 50% or less compared to the allergenic activity of naturally occurring Bet v 1 allergen.

The Examiner relies, in part, on the following evidence:

Valenta et al.	WO 99/16467	Apr. 8, 1999
Nishiyama et al.	US 6,187,311 B1	Feb. 13, 2001

Susanne Vrtala et al., *T Cell Epitope-Containing Hypoallergenic Recombinant Fragments of the Major Birch Pollen Allergen, Bet v 1, Induce Blocking Antibodies*, 165 J. IMMUNOL. 6653-6659 (2000) ("Vrtala 2000").

STANLEY L. HEM & JOE L. WHITE, VACCINE DESIGN: THE SUBUNIT AND ADJUVANT APPROACH 249-276 (1995).

Appellants rely on the following evidence:

Susanne Vrtala et al., *Genetic Engineering of the Major Timothy Grass Pollen Allergen, Phl p 6, to Reduce Allergenic Activity and Preserve Immunogenicity*, 179 J. IMMUNOL. 1730-1739 (2007) ("Vrtala 2007").

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[2] Claims 24-32 are also pending, but have been withdrawn from consideration. Claims 1-23, 35, 36, 42, 47, and 51 have been canceled.

The claims stand rejected as follows:

(A) Claims 33, 34, 37-41, 43-46, 48-50, and 52-54 under 35 U.S.C. § 112, first paragraph as lacking enablement.

(B) Claims 33, 34, 37-41, 43-46, and 48-50 under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support.

(C) Claims 33, 34, 37-40, 43-46, 48, 49, 53, and 54 under 35 U.S.C. § 102(b) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as unpatentable over Vrtala 2000.

(D) Claims 33, 34, 37, 46, 48-50, and 52-60 under 35 U.S.C. § 103(a) as unpatentable over Valenta as evidenced by Vrtala 2000.

(E) Claims 33, 49, 50, 55-57, 59, and 60 under 35 U.S.C. § 103(a) as unpatentable over Vrtala 2000 and Hem.

(F) Claims 33, 38, and 41 under 35 U.S.C. § 103(a) as unpatentable over Vrtala 2000.

(G) Claims 33, 38-41, 43-45, and 56 under 35 U.S.C. § 103(a) as unpatentable over Valenta.

REJECTION A

The Examiner rejected claims 33, 34, 37-41, 43-46, 48-50, and 52-54 as non-enabled. According to the Examiner,

> [T]he specification, while being enabling for methods of treating birch allergy by administering trimers of Bet v 1, administering amino acid fragment 1-73 of Bet v 1, or amino acid fragment 74-159 of Bet v 1, does not reasonably provide enablement for the treatment or prevention of IgE mediated disorders resulting from exposure to the major allergens of alder, birch, and hazel by administering derivatives of Bet v 1.

(Ans. 5.)

According to the Examiner, the claims can be interpreted as requiring that "the therapeutic method is 100% effective in 100% of patients" and that "the development of an allergen specific IgE response never occurs" (Ans. 6). The Examiner argues that "specific immunotherapy is not effective in all patients, and even when treatment is clinically effective, the majority of patients demonstrate decreased severity of IgE mediated disorders, rather than the prevention and complete cessation of IgE-mediated disorders" (*id.* at 7). Along the same lines, the Examiner argues that "unique epitopes can be found that are not present in . . . all Fagales (which includes birch, alder, and hazel) pollens and as such crossreactivity of a derivative is not guaranteed" for all birch, alder, and hazel pollens (*id.* at 6-7).

In addition, the Examiner argues that the claims are not enabled because "the only identifiable patients in need of treatment are those . . . currently hav[ing] an ongoing IgE-mediated immune response . . . and as such the IgE-mediated reaction cannot be prevented because it has already occurred" (*id.* at 6).

Finally, the Examiner argues that the three hypoallergenic Bet v 1 derivatives exemplified in the Specification are not representative of the broad range of Bet v 1 derivatives encompassed by the claims. The Examiner argues that "a skilled artisan would need to rely on trial and error to identify derivatives suitable for use in the recited method" (*id.* at 8). Since "trial and error . . . is random and unpredictable, . . . a skilled artisan would need to perform an undue amount of research prior to practicing the full breadth of applicant's claimed method" (*id.*).

Issues

Is the Examiner's standard for compliance with the enablement requirement reasonable?

Has the Examiner established that it would have required undue experimentation to identify hypoallergenic derivatives of the Bet v 1 allergen, other than the three derivatives exemplified in the Specification?

Findings of Fact

1. A hypoallergenic derivative of an allergenic protein "has a reduced allergenic activity compared with an allergenic protein from which it is derived" (Spec. 2). "It is preferred that the derivative of an allergenic protein leads to induction of IgG antibodies . . . [and] does not elicit a significant IgE response" (*id.* at 4).

2. According to the Specification:

> [A]llergenic activity of a sample is determined by determining the IgE antibodies which are induced in a test animal upon application of the sample. The allergenic activity is preferably defined in suitable in vitro or in vivo tests. A preferred in vitro test is the basophil histamine release assay . . . Alternatively the allergenic activity is determined in a skin test . . .

(Spec. 4).

3. The Specification teaches that a hypoallergenic derivative of the birch pollen allergen, Bet v 1, "may be a fragment of the wildtype protein or an oligomer thereof. The derivative may also be a peptide or a molecule which results from site directed mutagenesis. It is also possible to chemically modify the naturally occurring wildtype allergenic protein" (Spec. 2-3).

4. The Specification discloses three hypoallergenic derivatives of the Bet v 1 pollen allergen: a recombinant fragment comprising amino acids 1-73 of the Bet v 1 allergen; a fragment comprising amino acids 74-159 of Bet v 1; and a recombinant trimer consisting of three covalently-linked copies of Bet v 1a" (Spec. 8).

5. According to the Specification, "genetically modified rBet v 1 derivatives induced IgG antibodies to rBet v 1 wildtype and to Bet v 1-homologous allergens . . . [and] mouse-derived antibodies strongly inhibited the binding of birch pollen allergenic patients' IgE to Bet v 1" (Spec. 5).

Discussion

"Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003). *See also In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (claims to method of "restoring hair growth" encompassed achieving full head of hair but did not require it).

We agree with Appellants that the Examiner's rejection is based on an overly stringent standard for enablement. While the claims might encompass a therapeutic method that is 100% effective against all alder, birch, and hazel allergens in all patients, they do not require it. Moreover, we don't agree with the Examiner that the claims require treating subjects prior to any initial allergic reaction. We see no reason why treating or preventing a *subsequent* IgE-mediated response in a subject who has already experienced an allergic reaction would not be encompassed by the claims.

Further, "to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention

without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). "That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). Some experimentation, even a considerable amount, is not "undue" if, for example, the specification provides a reasonable amount of guidance as to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

In this case, the Specification teaches that the starting point is a known protein, the wildtype Bet v 1 allergen, and that derivatives can be made by various conventional methods (FF3). Moreover, the Specification discloses a number of well known assays to determine whether a given derivative is suitable for use in the claimed method (FF2). While making derivatives of the native Bet v 1 sequence (by conservative amino acid substitution, deletion, fragmentation, etc.) and testing them for allergenicity may be time consuming and tedious, the Examiner has not established that it would have been anything more than routine for one skilled in the art, given the guidance in the Specification.

The Examiner has not established that undue experimentation would have been required to practice the claimed method.

The rejection of claims 33, 34, 37-41, 43-46, 48-50, and 52-54 for lack of enablement under the first paragraph of 35 U.S.C. § 112 is reversed.

REJECTION B

The Examiner rejected claims 33, 34, 37-41, 43-46, and 48-50 as failing to comply with the written description requirement.

Claim 33 is directed to administering one or more derivatives of Bet v 1 to a patient, wherein the derivatives induce IgE-blocking antibodies, and wherein the allergenic activity of the derivative is 50% or less than naturally occurring Bet v 1.

The Examiner finds that "the term 'derivative' has been defined very broadly" (Ans. 11) in the Specification, and includes "fragments, oligomers, and chemically modified forms of naturally occurring allergens as well as molecules obtained by site directed mutagenesis of an allergen protein" (*id.* at 10). According to the Examiner, the three examples disclosed in the Specification, "two of which are truncations of the natural allergen (aa1-73 and aa74-159) and one of which is a trimer of the naturally occurring Bet v 1 allergen" (*id.*), "are not structurally representative of [the] full breadth of the recited genus" (*id.*). Moreover, "the specification does not teach how the recited functional properties are correlated with structure of the disclosed species" (*id.*).

Issue

Ha the Examiner established that the three hypoallergenic derivatives of the Bet v 1 allergen exemplified in the Specification are not representative of the genus of Bet v 1 allergens encompassed by the claims?

Discussion

We disagree with the Examiner's assertion that the disclosed species are not representative of the genus of hypoallergenic polypeptides required by the claims, or that the disclosed species are not sufficient to show that Appellants were in possession of the required genus. Again, the Specification teaches that the starting point for the genus is a known protein, the wildtype Bet v 1 allergen, and that derivatives can be made by various

conventional methods (FF3). One of skill in the art would immediately envision that functional polypeptides would include other fragments of wildtype Bet v 1, polypeptides with conservative substitutions, polypeptides with minor deletions, etc., that largely retain the structure of wildtype Bet v 1 allergen.

The rejection of claims 33, 34, 37-41, 43-46, and 48-50 for lack of written descriptive support under the first paragraph of 35 U.S.C. § 112 is reversed.

REJECTION C

The Examiner rejected claims 33, 34, 37-40, 43-46, 48, 49, 53, and 54 as anticipated by, or in the alternative, as unpatentable over Vrtala 2000. Appellants have not presented separate arguments for the claims. Therefore, we select claim 33 as representative of the claims subject to this rejection, and the remaining claims will stand or fall accordingly. 37 C.F.R. § 41.37(c)(1)(vii).

The Examiner's findings of fact regarding the teachings of the prior art (Ans. 12-13) are not in dispute, and we adopt them as our own. We agree that the claims are not patentable over the prior art for the reasons given by the Examiner, and are not persuaded otherwise by Appellants' arguments.

Appellants contend that Vrtala 2000 "only uses specifically identified Bet v 1 fragments and thus fails to demonstrate the general principles of the immunotherapeutic utility of a broad range of Bet v 1 allergens including fragments AND oligomers" (App. Br. 28). Similarly, Appellants contend that Vrtala 2000 "dealt only with the isolated fragments and not the fragment mix for vaccination" (*id.*).

These arguments are not persuasive because there is no dispute that Vrtala 2000 discloses administering Bet v 1 fragments (indeed the same fragments disclosed in the present Specification) and claim 33 (like all the other claims) merely requires administering "one or more immunotherapeutic agents derived from Bet v 1." Thus, as pointed out by the Examiner, "the claims require administration of only a single agent" (Ans. 23), and don't require a mixture of fragments or oligomers.

Appellants also contend that Vrtala 2000 "uses mainly complete and incomplete Freunds Adjuvant (CFA, ICFA) which is not allowed for human use," and it wouldn't have been obvious to substitute alum for Freunds Adjuvant because Vrtala 2007 "demonstrated that hypoallergens given with CFA fail to induce allergen-specific IgG when adsorbed to Alum" (App. Br. 28-29).

However, as pointed out by the Examiner, "Vrtala [2000] et al. explicitly state that they will be conducting clinical trials [in humans] using their disclosed fragments" (Ans. 24), and in any case, claims reciting administration in alum (*id.*) are not included in rejection C. Moreover, as also noted by the Examiner, Vrtala 2007 "discloses administration of an allergen that is not Bet v 1 and discloses that one of the fragments when absorbed onto alum *did* induce allergen specific IgG" (*id.* at 27).

Finally, Appellants contend that "[t]he recited dosage levels and the periodicity schedule are not subject to routine optimization . . . [and] it is experimentally intensive and critical to successful immunotherapy" (App. Br. 29).

Again, as pointed out in more detail by the Examiner on page 25 of the Examiner's Answer, Vrtala 2000 teaches "the dosages recited in the

instant claims" and also teaches a series of four monthly administrations of Bet v 1 derivatives in mice (Ans. 25). Appellants have not provided any evidence to establish that adapting the dosage and administration schedule for humans would have required anything more than routine optimization.

The rejection of claims 33, 34, 37-40, 43-46, 48, 49, 53, and 54 as anticipated by, or in the alternative, as unpatentable over Vrtala 2000 is affirmed.

REJECTION D

The Examiner rejected claims 33, 34, 37, 46, 48-50, and 52-60 under 35 U.S.C. § 103(a) as unpatentable over Valenta as evidenced by Vrtala 2000.

With respect to Valenta, Appellants contend that "nothing is mentioned . . . of the periodicity element of claim 33 nor was the '50% or less' hypoallergenic activity established as a therapeutic threshold" (App. Br. 29). With respect to Vrtala 2000, Appellants refer to their previous arguments (*id.*).

Appellants' arguments are not persuasive. As pointed out by the Examiner, Valenta discloses monthly "administrations of Bet v 1 trimers to mice" (Ans. 26; Valenta 11). In addition, the Examiner relies on Valenta's explicit disclosure of "specific hyposensitization therapy . . . [which] encompasses administering repeatedly to the mammal, typically a human . . . suffering from type I allergy against the protein allergen an immunogen that is capable of raising an IgG immune response against the protein antigen" (Valenta 5: 32 to 6: 1; Ans. 26) as evidence that Valenta discloses periodic administration of hypoallergens as required by claim 33. We agree that this is consistent with the "periodicity element of claim 33." "With regard to the

50% or less activity limitation" of claim 33, the Examiner points out that Valenta's trimers of Bet v 1 are the same as those disclosed in the present Specification, and "it is inherent that the trimers of Bet v 1 comprise the recited activity" (Ans. 26). Finally, Appellants' arguments with respect to Vrtala 2000 are not persuasive for the reasons discussed above.

The rejection of claims 33, 34, 37, 46, 48-50, and 52-60 as unpatentable over Valenta as evidenced by Vrtala 2000 is affirmed.

REJECTIONS E-G

The Examiner rejected claims 33, 49, 50, 55-57, 59, and 60 as unpatentable over Vrtala 2000 and Hem; claims 33, 38, and 41 as unpatentable over Vrtala 2000; and claims 33, 38, and 41 as unpatentable over Vrtala 2000.

With respect to each of these rejections, Appellants rely on "[t]he foregoing arguments" (App. Br. 30).

These arguments are not persuasive for the reasons discussed above.

SUMMARY

We reverse enablement and written description rejections A and B, and affirm prior art rejections C-G.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

dm

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